Dose Considerations in the SO_2-Exposed Exercising Asthmatic

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In this study we have demonstrated that by combining data from several recent controlled human exposure studies it is possible systematically to relate increases in airways resistance to the rate of SO_2 exposure (D_{min}) in the exercising asthmatic. It was determined that the mode of SO_2 exposure (oral vs. oronasal) greatly influences the degree of response in the asthmatic. Forced oral breathing consistently produces larger percentage increases in SR_{aw} per unit increase in SO_2 exposure rate. We have demonstrated further that while the dose/effect relationship which describes the increases in specific airways resistance (SR_{aw}) versus exposure rate (D_{min}) of SO_2 is most consistently exponential in character, a linear (more conservative) model also can be used to fit the data.

Using both the linear and exponential model, we have constructed a matrix which allows direct estimation of the combined minute ventilation $(\dot{V}_E)$ and SO_2 concentration (as ppm or µg/L) required to achieve various levels of specific airways resistance increase. In this report this matrix is constructed only on subjects breathing in an unencumbered (oronasal) manner. Future reports will explore these relationships in the asthmatic breathing in an encumbered (oral) manner.

Introduction

Based upon data from several recently conducted controlled human exposure studies (1-5), it has been demonstrated that asthmatic subjects exposed to SO_2 respond with an increase in specific airways resistance. It has been demonstrated further that when exposure is combined with exercise, at a light to moderate level, the magnitude of the SO_2-induced increase is greater.

Based upon what is known concerning the asthmatic and within the context of the clinical definition of this disease, this effect of SO_2 exposure, especially when combined with exercise, is not unexpected.

The current results of controlled human exposure studies in which exercising asthmatic subjects were exposed to SO_2 during exercise can be divided into two groups: studies of subjects exposed via a mouthpiece which precludes nasal breathing and thus forces SO_2 uptake to be exclusively oral (encumbered breathing) or studies of subjects exposed via a facemask or in a chamber which permits oronasal (unencumbered) breathing.

Under these circumstances, the exercising asthmatic who is exposed exclusively by mouthpiece (encumbered) represents the most severe or "worst case" exposure situation. In the study reported herein, this group will be focused on initially. Their airways resistance responses will then be compared to those observed in asthmatics exposed in an unencumbered manner.

Approach

The approach used in this study is the same as has been reported previously (6-8). To briefly summarize, observed changes in airways resistance expressed as specific airways resistance (SR_{aw}) are calculated as a percentage increase (or decrease) from the control (pre-exposure) value with both individual and sets of subjects serving as their own control. For each data set, individual subject and group mean values for percentage changes in SR_{aw} ($\%\Delta\ SR_{aw}$) are calculated and represent the "effect" (or dependent) variable. Since the method by which increases in SR_{aw} are

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presented is not always consistent among the various investigators, for convention we have chosen to utilize a uniform method of calculation which allows direct interexperimental comparisons to be made. Briefly described our method utilizes the pre- and post-exposure SR_{aw} values from each subject or group of subjects exposed to various levels of SO_2 as the basis for estimation of $\%\Delta\ SR_{aw}$. From this $\%\Delta\ SR_{aw}$ is subtracted the percentage of change observed when the same subjects are exposed to air alone (an SO_2 concentration of zero). Another means by which $\%\Delta\ SR_{aw}$ can be determined is to utilize the air only (sham) exposure values as the overall baseline for all subjects regardless of day of exposure. However, after investigating this approach, we concluded that it fails to account for the observed daily variations in pre-exposure SR_{aw} which occurs in asthmatic subjects.

The choice of the dose parameter also provided opportunity for investigation. In the first instance it is not possible from any studies conducted thus far to absolutely quantify the dose of SO_2 delivered to the target tissue or organ. However, attempts at developing extrapolation methods are currently in progress (8, 9) and although they appear promising, none has as yet been empirically confirmed. Consequently, the forms in which SO_2 exposure can be expressed are either as concentration alone (ppm, $\mu g/m^3$, $\mu g/L$), the product of concentration and exposure duration $(C \times T)$ or the product of concentration and minute ventilatory volume (provided $\dot{v}_E$ is known or estimatable) with or without temporal factors. Since neither the concentration alone, nor the concentration times exposure duration $(C \times T)$ expression can account for the influence of changes in minute ventilation $(\dot{v}_E)$ that accompany increased exercise, we elected not to explore them further. Alternatively, the use of several forms utilizing the product of concentration and V_E were explored. Remembering that $\dot{V}_E$ is expressed as liters/minute, several equations can be derived which combine SO_2 concentration and $\dot{V}_E$ with or without temporal factors.

SO_2 concentration ($\mu g/m^3/1000$) $\times$ $\dot{V}_E$ (L/min) =
$$\mu g/min\ SO_2 \quad (1)$$

Since $(\mu g/m^3)/1000 = \mu g/L$,

SO_2 concentration ($\mu g/L$) $= \dot{V}_E \times \mu g/min\ SO_2$ (2)

SO_2 concentration (ppm) $\times$ $\dot{V}_E$ (L/min) =
$$ppm\text{-}L/min\ SO_2 \quad (3)$$

SO_2 concentration (ppm as $\mu L/L$) $\times$ $\dot{V}_E$ (L/min) =
$$\mu L/min\ SO_2$$

When consideration is given to temporal factors,

either $\mu g/min$ or $\mu L/min$ can be multiplied by the total minutes of exposure. The resultant products are total μg or total μL.

$$\mu g/min \times \text{minutes of exposure} = \text{total } \mu g\ SO_2 \quad (5)$$

$$\mu L/min \times \text{minutes of exposure} = \text{total } \mu L\ SO_2 \quad (6)$$

We have adopted for our purposes Eqs. (2) and (5). This was done because it was concluded that a mass measurement (μg) was preferred to a volumetric (ppm) one, particularly when comparison with other airborne pollutants is desired. We have labeled the resultant of Eq. (2) D_{min} ($\mu g/min$), and that of Eq. (5) D_t (μg). It should be noted that D_{min} is actually an exposure rate, while D_t is a total exposure dose. Also, since $\dot{V}_E$ is normally expressed as L/min, the concentration form of $\mu g/L$ was adopted over $\mu g/m^3$, although this latter form is that in which ambient levels are normally expressed. It was reasoned that the use of $\mu g/L$ allows a more direct estimate of D_{min} by simply combining $\dot{V}_E$ in L/min and concentration as $\mu g/L$.

Based on previous studies (6-8) we observed that changes in airways resistance (expressed as either R_{aw} or SR_{aw}) in response to SO_2 exposure vary most consistently with the exposure rate (D_{min}). In fact, D_t is normally found to correlate very poorly. In the studies reported herein, D_{min} (exposure rate) was also found to correlate better with changes in SR_{aw} and thus will be used as the dose (or independent) variable.

For each set of data, D_{min} and $\%\Delta\ SR_{aw}$ are calculated and a scatter plot of D_{min} (x axis) versus $\%\Delta\ SR_{aw}$ (y axis) values is prepared. To these points a series of curve-fitting equations is applied for the purpose of determining which mathematical relationship best fits these data points and which serve as the basis for prediction of changes in $\%\Delta\ SR_{aw}$ in a broader context.

Since the issue of the choice of the most applicable mathematical relationship is an important one, we will briefly discuss our approach to making this choice. There are a large number of mathematical relationships (equations) which can be applied to any set of data points, either in the normal or transformed state. Thus, a series of guidelines must be adopted which will assist in selecting the correct form of the equation to be used. We have adopted the guidelines set out by Daniel and Wood (10). The method of fitting equations to data which we have utilized is an adaptation of both the Linwood and non-Linwood least-squares fitting program which has been widely documented and is available to multiple users.

As a working principle we have adopted the approach of favoring the equation with the least

number of constants which provides the best fit. In some cases alternative equations are also chosen to visualize the dose/effect relationship as well. These cases are noted and the rationale for their exploration and use discussed. It should be noted also that we have utilized group mean values of %Δ SR$_{aw}$ to prepare our scatter plots and as the basis of analysis. In a previous report (8) we have presented data which compare the results obtained utilizing both group mean values and individual subject changes in %Δ SR$_{aw}$.

Results

Table 1 summarizes the percent changes in SR$_{aw}$ reported in exercising asthmatic subjects exposed to SO$_2$ via a mouthpiece (encumbered) along with group mean $\dot{V}_E$ values. In addition, the author and reference are listed. The broader set of data from which these summary values are derived appear in Table 2. As can be observed, there is a progressive increase in %Δ SR$_{aw}$ as exposure rate (D_{min}) increases. By the application of linear regression analysis (11, 12) (see Table 3 for details), the coefficient of correlation r was estimated to be 0.9605, and the coefficient of determination r^2 was estimated to be 0.9225. Stated

simply, it is observed that in this body of data which relates SO$_2$ D_{min} to %Δ SR$_{aw}$ in the exercising asthmatic that D_{min} correlates well with %Δ SR$_{aw}$.

Figure 1 illustrates the results obtained when both a linear equation and exponential equation are fitted to the data points. It should be noted that the exponential equation provides a better fit to the points than the linear. In this latter case, the exponential coefficients are $r = 0.9927$ and $r^2 = 0.9855$.

As we discussed previously, a number of equations can be fitted to these data points. In this specific case both an exponential and geometric (power) equation were found to fit the observed data points best. However, the choice of which equation to use for curve fitting requires further distinction.

In general, exponential least squares is favored when a plot of log y (%Δ SR$_{aw}$) versus x (D_{min}) is linear in form. Alternatively, a geometric (power) least-squares equation is favored when a plot of log y versus log x is linear. A test of both equations revealed that for the appropriately log transformed data the exponential equation provided the better linear fit. Although it contains more constants than the geometric (power) form,

Table 1. Response of specific airways resistance (SR$_{aw}$) to SO$_2$ for asthmatic subjects exercising, encumbered breathing (summary data).

SO$_2$ concn, μg/L	$\dot{V}_E$, L/min	%Δ SR$_{aw}$	D_{min}, μg/min	Exposure mode	Investigator
0.65	35	32	23	Oral	Sheppard (1)
1.3	27	63	35	Oral	Linn (2)
1.3	35	115	46	Oral	Sheppard (1)
1.3	40	126	53	Oral	Kirkpatrick (3)
1.95	40	320	78	Oral	Linn (2)
2.6	31	418	81	Oral	Sheppard (1)

Table 2. Response of specific airways resistance (SR$_{aw}$) to SO$_2$ for asthmatic subjects exercising, encumbered breathing (group mean data).

	Sheppard (1)	Sheppard (1)	Linn (2)	Kirkpatrick (3)	Linn (2)	Sheppard (1)
SO$_2$ concn						
ppm	0.25	0.5	0.5	0.5	0.75	1
μg/L	0.65	1.3	1.3	1.3	1.95	2.6
SR$_{aw}$ (A), pre-exposure						
Mean	8.07	8.46	4.62	6.81	4.92	4.76
Std. dev.	2.96	3.58	1.78	4.06	2.05	0.98
SR$_{aw}$ (B), post-exposure						
Mean	10.48	18.16	9.08	16.44	23.23	24.35
Std. Dev.	4.49	10.05	3.01	9.04	13.3	8.58
Net change, A-B	2.41	9.7	4.46	9.63	18.31	19.59
Change, % (exposure)	30	115	97	141	375	412
Change, % in controls	–2	0	34	15	55	–5
Net % change, SO$_2$—controls	32	115	63	126	320	418
V_E, L/min	35	35	27	41	40	31
D_{min}, μg/L	23	46	35	53	78	81

Table 3A. Regression results: D_{min} vs. $\%\Delta\ SR_{aw}$ for exercising asthmatics (encumbered breathing).

|		Mean	Standard deviation
Independent variable	D_{min}	52.633	23.209
Dependent variable	SR_{aw}	179.000	154.254

Table 3B. Dependent variable: $\%\Delta\ SR_{aw}$

Variable	Regression coefficient	Standard error	$F(1,4)$
D_{min}	6.3836	0.9253	47.596
Constant	−156.9877		

Standard error of estimate = 48.0192

$r^2 = 0.9225$

$r = 0.9605$

Table 3C. Analysis of variance.

Source	Sum of squares	D.F.	Mean square	F ratio
Regression	109748.6107	1	109748.6107	47.5958
Residual	9223.3893	4	2305.8473	
Total	118972.000	5		

Table 3D.

	Observed	Calculated	Residual
1	32.000	−11.443	43.443
2	63.000	66.437	−3.437
3	115.000	136.656	−21.656
4	126.000	181.341	−55.341
5	320.000	340.929	−20.929
6	418.000	360.080	57.920
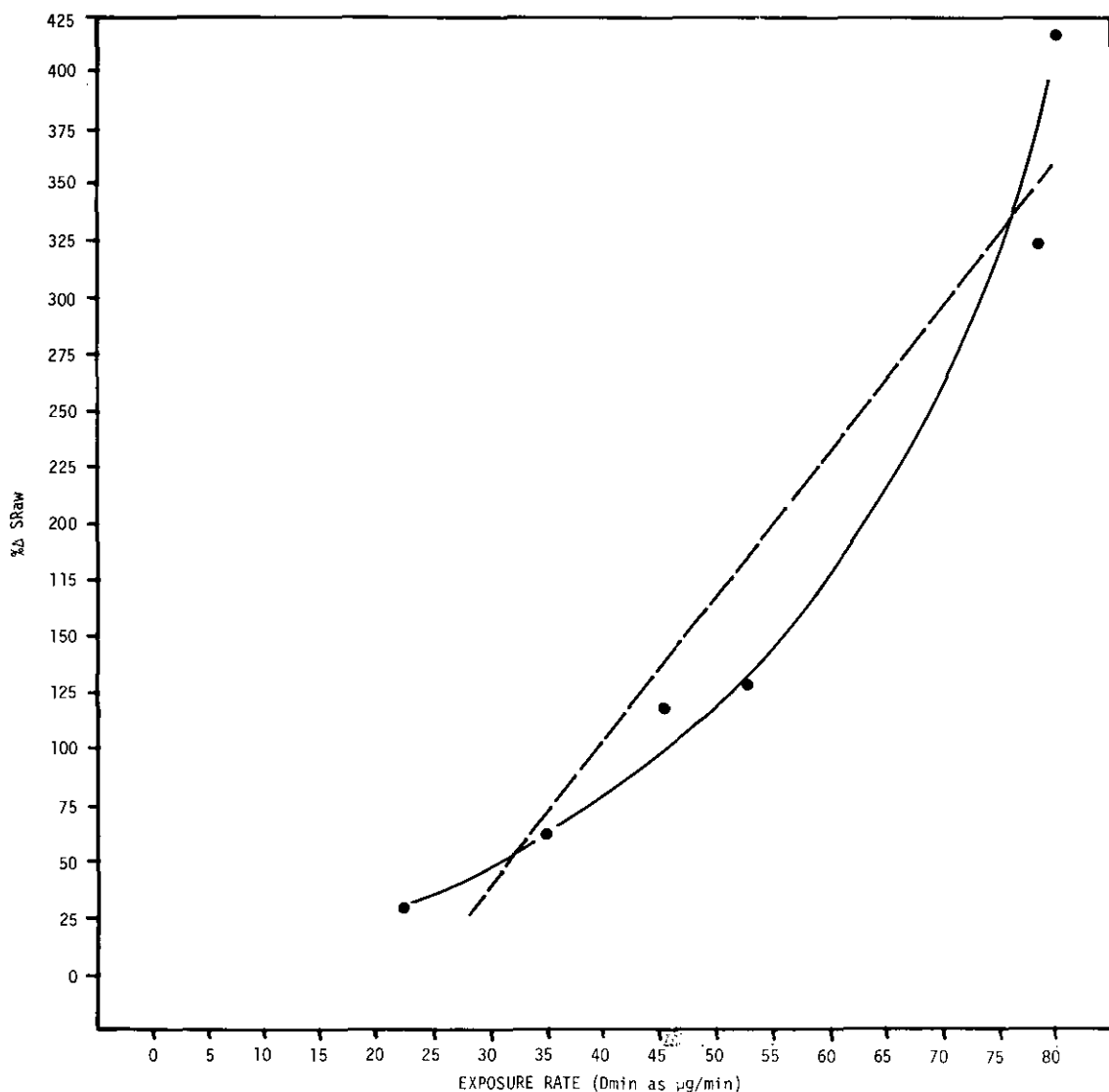
FIGURE 1. Response of the exercising asthmatic to SO_2 (encumbered breathing): (●) observed; (− −) linear best fit curve; (—) exponential best fit curve. Equations: linear, $y = a + bx$, $y = -157 + 6.4x$ ($r^2 = 0.923$); exponential, $y = ae^{bx}$, $y = 14e^{0.04x}$ ($r^2 = 0.986$).

its use is dictated in this context. As such we conclude that an exponential equation of the form $y = ae^{bx}$ most accurately describes the relationship between D_{min} and $\%\Delta\ SR_{aw}$ in this set of data on exercising asthmatics.

As noted, a simple linear equation can be fitted to these data points as well but displays the relationship less accurately. The decision to include it in Figure 1 and in subsequent calculations was based on the fact that over this range of SO_2 exposure rate (D_{min}) values it generally predicts a higher $\%\Delta\ SR_{aw}$ per unit increase in D_{min}. Thus it can be used to represent a more conservative or "worst case" model for prediction purposes. In later sections wherein the application of the model is discussed this distinction should be kept in mind.

Even with modeling considerations aside, it is clear that data derived from controlled study of SO_2 exposures to exercising asthmatics breathing in an encumbered mode indicate a consistent and positive relationship between increases in exposure rate (D_{min}) and specific airways resistance ($\%\Delta\ SR_{aw}$) increases.

As we have stated previously, several other authors have chosen to investigate this relationship in asthmatic subjects allowed to breath in an unencumbered manner, reasoning that it is more reflective of ambient circumstances (2-5). We have evaluated these data as well, and they are summarized in Table 4 (derived from Table 5). Figure 2 illustrates both the fitted linear and exponential curves. In this case the previous pattern observed with the encumbered breathing subjects is repeated, i.e., the exponential equation most accurately reflects the dose/effect relationship, and D_{min} is shown to be highly correlated to $\%\Delta\ SR_{aw}$ (see Table 6).

There is, however, a crucial and very important difference between the changes observed in the unencumbered breathers and those observed in encumbered breathers. In the case of encumbered breathers, the exercising asthmatic subjects demonstrate a consistently larger $\%\Delta\ SR_{aw}$ increase per unit D_{min} increase than the unencumbered breathing subjects. This larger response per unit D_{min} is particularly noted at the higher exposure rate levels and is vividly illustrated in Figures 3 and 4, wherein both the best fit linear and exponential curves are compared as a function of expo-

Table 4. Response of specific airways resistance (SR_{aw}) to SO_2 for asthmatic subjects exercising, unencumbered breathing (summary data).

SO_2 concn, μg/L	$\dot{v}_E$, L/min	$\%\Delta\ SR_{aw}$	D_{min}, μg/min	Exposure mode	Investigator
0.65	27	1.0	18	Oronasal	Linn (2)
0.52	48	1.0	25	Oronasal	Linn (5)
1.3	27	5.5	35	Oronasal	Linn (2)
1.04	48	33	50	Oronasal	Linn (5)
1.3	42	54	55	Oronasal	Kirkpatrick (3)
1.56	48	118	75	Oronasal	Linn (5)
1.95	40	185	78	Oronasal	Linn (4)

Table 5. Response of specific airways resistance (SR_{aw}) to SO_2 for asthmatics exercising, unencumbered breathing (group mean data).

	Linn (5)	Linn (2)	Linn (5)	Linn (2)	Kirkpatrick (3)	Linn (5)	Linn (4)
SO_2 concn							
ppm	0.2	0.25	0.4	0.5	0.5	0.6	0.75
μg/L	0.52	0.65	1.04	1.3	1.3	1.56	1.95
SR_{aw} (A), pre-exposure							
Mean	5.95	4.00	5.35	4.33	7.35	5.47	4.96
Std. dev.	2.92	ND	2.52	ND	3.61	2.45	1.62
SR_{aw} (B), post-exposure							
Mean	8.15	4.54	9.06	5.13	12.44	13.92	16.89
Std. dev.	4.16	ND	5.31	ND	5.89	8.70	9.45
Net change, A-B	2.22	0.54	3.71	0.8	5.09	8.45	11.93
Change, % exposure	37.5	14	69	18.5	69	154	240
Change, % in controls	36	13	36	13	15	36	55
Net % change, SO_2—controls	1.0	1.0	33	5.5	54	118	185
V_E, L/min	48	27	48	27	42	48	40
D_{min}, μg/min	25	18	50	35	55	75	78

Table 6A. Regression results: D_{min} vs. $\%\Delta \, SR_{aw}$ for exercising asthmatics (unencumbered breathing).

		Mean	Standard deviation
Independent variable	D_{min}	47.943	23.467
Dependent variable	$\%\Delta \, SR_{aw}$	56.857	70.188

Table 6B. Dependent variable: $\%\Delta \, SR_{aw}$

Variable	Regression coefficient	Standard error	$F(1,5)$
D_{min}	2.7439	0.5323	26.573
Constant	−74.6950		

Standard error of estimate = 30.5970

$r^2 = 0.8416$

$r = 0.9174$

Table 6C. Analysis of variance.

Source	Sum of squares	D.F.	Mean squares	F ratio
Regression	24877.4701	1	24877.4701	26.5735
Residual	4680.8870	5	936.1774	
Total	29558.3571	6		

Table 6D.

	Observed	Calculated	Residual
1	1.000	−26.402	27.402
2	1.500	−6.097	7.597
3	5.500	21.343	−15.843
4	33.000	62.502	−29.502
5	54.000	76.221	−22.221
6	118.000	131.100	−13.100
7	185.000	139.332	45.668
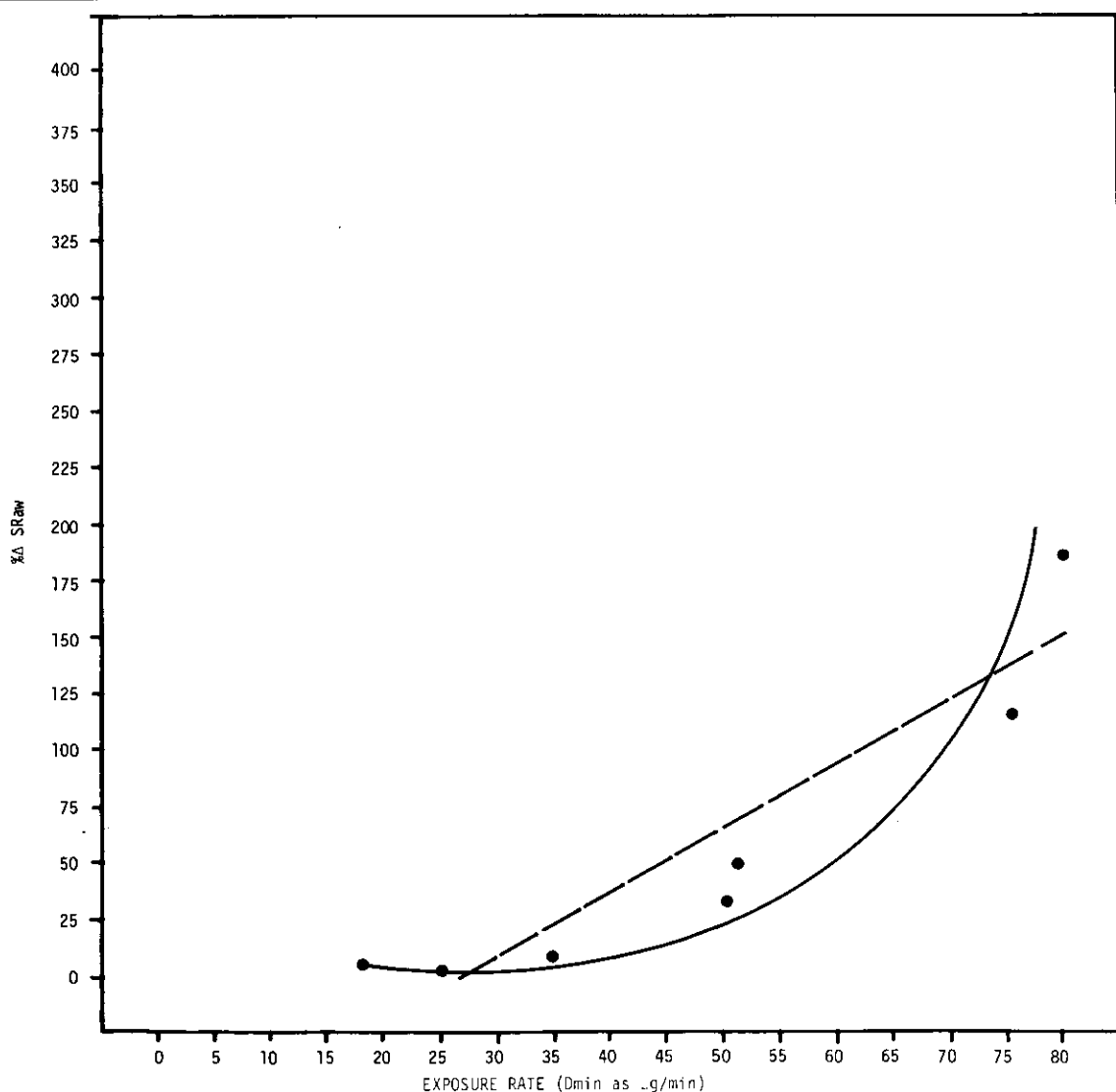
FIGURE 2. Response of the exercising asthmatic to SO_2 (unencumbered breathing): (•) observed; (− −) linear best fit curve; (—) exponential best fit curve. Equations: linear, $y = a + bx$, $y = -74 + 2.74x$ ($r^2 = 0.842$); exponential; $y = ae^{bx}$, $y = 0.24e^{0.09}$ ($r^2 = 0.963$).

sure mode. In both figures, A represents the encumbered breathing asthmatic and B the unencumbered.

Inasmuch as the differences between the result obtained with the two exposure modes are not trivial, a decision must be made for the future as to which exposure conditions are most adaptable for attempting an extrapolation of these data to the free-living asthmatic. At present we are evaluating this issue and are proceeding to examine results based on data obtained using both exposure modes. An examination of this issue is underway, and preliminary findings are discussed below.

Application of the Model

One key question that data in this form can address is concerned with exploring the interrelationships between minute ventilation (and by association level of activity), ambient SO_2 concentration and increased specific airways resistance in the asthmatic. To examine these interrelationships, we have assembled in Tables 7 and 8 data which provide an estimate of the ambient SO_2 level (ppm or $\mu g/L$), which when combined with exercise ($\dot{V}_E$) will result in exposure rates (D_{min}) that correspond to differing levels of increase in SR_{aw}. Initially, we have used only data derived
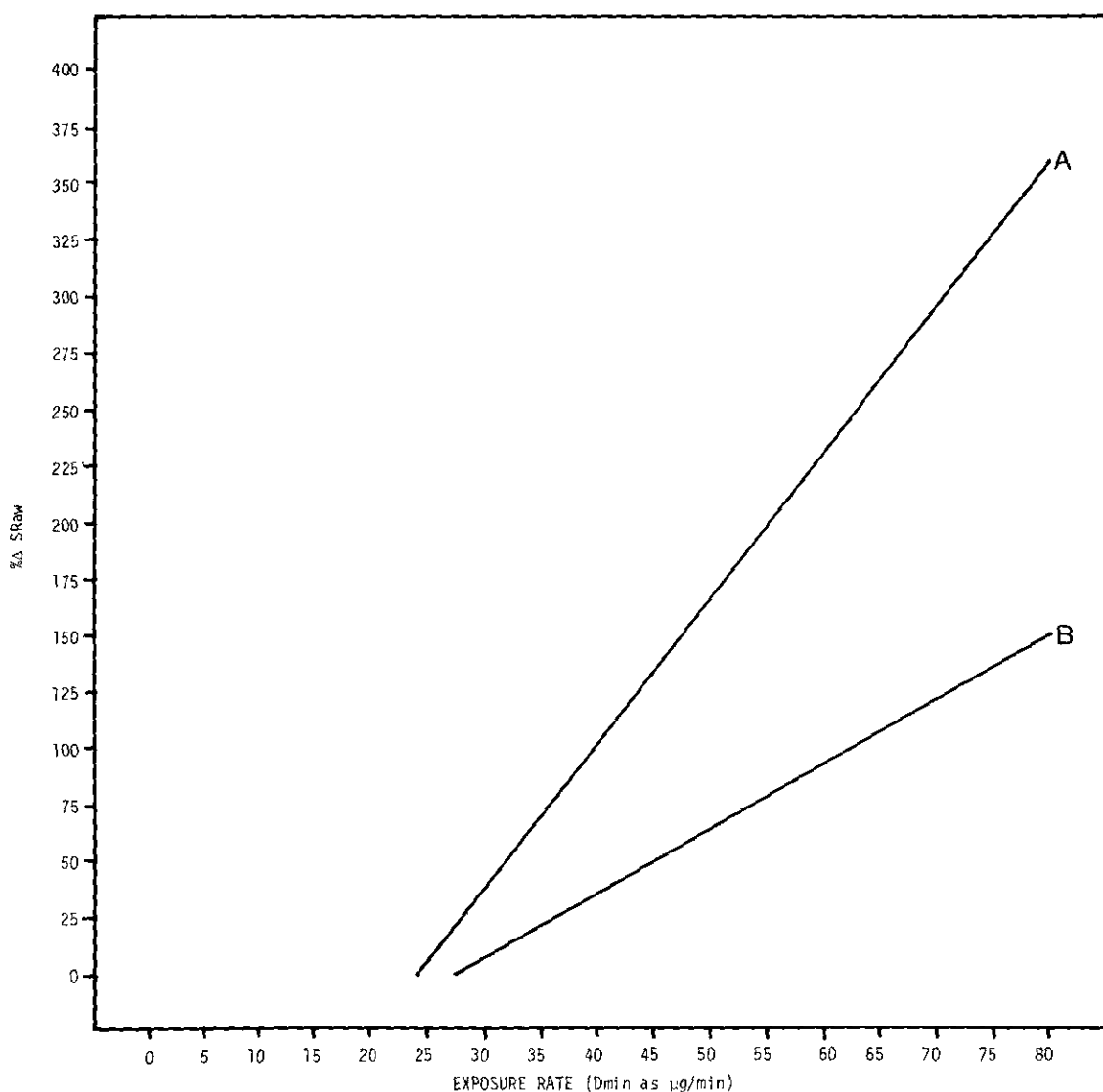
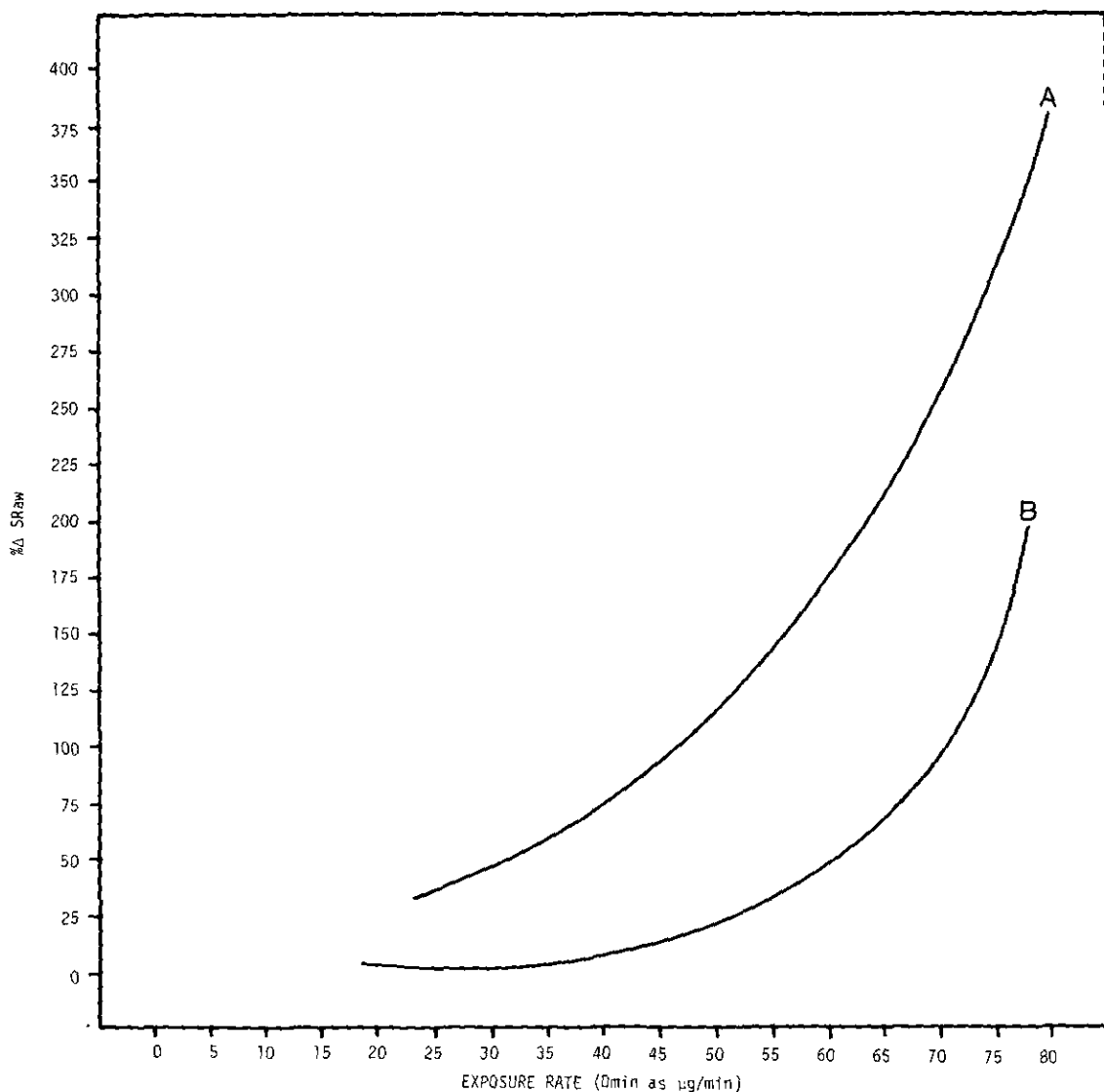
FIGURE 3. Comparison of the response of the exercising asthmatic to SO_2, encumbered vs. unencumbered breathing, (—) linear best fit curves: (A) encumbered breathing; (B) unencumbered breathing.

from studies of asthmatics breathing in an unencumbered mode. The data in Table 7 are derived from the D_{min} and %Δ SR_{aw} values obtained from the linear model and those in Table 8 from the exponential (see Fig. 2) model. They are constructed to illustrate the relationship between SO_2 concentration (as ppm or µg/L) and level of exercise ($\dot{V}_E$) at various levels of %Δ SR_{aw} (0-400) induced by the corresponding D_{min} values. For example, utilizing the D_{min} and %Δ SR_{aw} values derived from the linear equation, it is noted that in an asthmatic exercising at a light level ($\dot{V}_E$ = 20 L/min) a 0% increase in SR_{aw} would be predicted to occur at ambient SO_2 levels equal to or

less than 0.53 ppm (1.35 µg/L). The corresponding SO_2 level predicted from the exponential equation (Table 8) would be 0.577 ppm (1.50 µg/L).

As can be seen in Table 7, an increase of exercise to a moderate level ($\dot{V}_E$ = 40 L/min) lowers the SO_2 concentration required to achieve the 0% Δ SR_{aw} increase D_{min} value of 27 µg/min to 0.26 ppm (0.675 µg/L). Similar relationships are observed at all D_{min} and/or $\dot{V}_E$ values. An examination of Table 8 (values derived from the exponential equation) reveals the same pattern. Namely, as $\dot{V}_E$ increases, the SO_2 concentration required to achieve any increase in SR_{aw} (D_{min}) decreases.

In Figures 5 and 6 we have plotted a subset of

FIGURE 4. Comparison of the response of the exercising asthmatic to SO_2, encumbered vs. unencumbered breathing; (—) best fit exponential curves: (A) encumbered breathing; (B) unencumbered breathing.

these data as log (ln $\dot{V}_E$ vs. ln ppm) transformed values to achieve linearity. In this form the data provide a direct visualization of the $\dot{V}_E$ (level of exercise) combined with SO₂ concentration (as ppm) required to achieve any D_{min} (%Δ SR$_{aw}$) value.

Most importantly these figures illustrate the strong interdependence of $\dot{V}_E$ and concentration and thereby serve to underscore another important issue, namely, that regardless of which exposure mode is chosen to extrapolate to the free living asthmatic or, further, no matter which level of specific airways resistance increase is adjudged as adverse to the exercising asthmatic both activity level ($\dot{V}_E$) and SO₂ concentration (ppm or μg/L) must be addressed in the definition of acceptable ambient concentrations.

If, for example, 0.5 ppm SO₂ is chosen as that concentration which will be protective of the asthmatic, it can be clearly seen that this will be protective under some circumstances and not protective in others. Utilizing the more conservative linear model (Table 7, Fig. 5) if a zero increase in SR$_{aw}$ is desired the asthmatic will only be protected in an atmosphere of 0.5 ppm (1.3 μg/L) SO₂ when $\dot{V}_E$ values are at or below 20 L/min. At a 25% Δ SR$_{aw}$, the $\dot{V}_E$ value lies between 20 and 30; at 50% Δ SR$_{aw}$ between 30 and 40, and at 100% Δ SR$_{aw}$ between 40 and 50 L/min.

Stated another way, if it is assumed that a 50% increase in SR$_{aw}$ is the maximal tolerable change, it can be seen that this will be achieved over a wide range of SO₂ concentrations. However, if it is further required that the majority of subjects be

Table 7. Interrelationship of $\dot{V}_E$ and SO₂ concentration and D_{min} at various levels of %Δ SR$_{aw}$ for asthmatic subjects, exercising, unencumbered breathing (data derived from linear best fit curve).

$\dot{V}_E$, L/min	0% SR$_{aw}$, D_{min} 27		10% SR$_{aw}$, D_{min} 30.7		25% SR$_{aw}$, D_{min} 36.2		50% SR$_{aw}$, D_{min} 45.4		100% SR$_{aw}$, D_{min} 63.7		200% SR$_{aw}$, D_{min} 100		300% SR$_{aw}$, D_{min} 137		400% SR$_{aw}$, D_{min} 173	
	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm
10	2.70	1.03	3.07	1.18	3.62	1.39	4.54	1.75	6.37	2.45	10.00	3.85	13.7	5.27	17.3	6.65
20	1.35	0.520	1.54	0.590	1.81	0.69	2.27	0.873	3.19	1.23	5.00	1.92	6.85	2.63	8.65	3.33
30	0.900	0.350	1.02	0.390	1.21	0.464	1.51	0.581	2.12	0.815	3.33	1.28	4.56	1.75	5.76	2.22
40	0.675	0.260	0.767	0.290	0.905	0.348	1.14	0.436	1.59	0.611	2.5	0.962	3.43	1.32	4.32	1.66
50	0.540	0.210	0.614	0.240	0.724	0.278	0.908	0.349	1.27	0.488	2.00	0.769	2.74	1.05	3.46	1.33
60	0.450	0.170	0.511	0.197	0.603	0.232	0.756	0.291	1.06	0.408	1.66	0.638	2.28	0.877	2.88	1.11
70	0.380	0.150	0.438	0.170	0.517	0.198	0.648	0.249	0.910	0.350	1.43	0.55	1.96	0.754	2.47	0.950
80	0.340	0.130	0.384	0.150	0.453	0.174	0.568	0.218	0.796	0.306	1.25	0.481	1.71	0.658	2.16	0.831
90	0.300	0.110	0.341	0.130	0.402	0.155	0.504	0.194	0.708	0.272	1.11	0.426	1.52	0.585	1.92	0.738
100	0.270	0.100	0.307	0.120	0.362	0.139	0.454	0.175	0.637	0.245	1.00	0.385	1.37	0.527	1.73	0.665
110	0.250	0.094	0.279	0.110	0.329	0.127	0.413	0.159	0.579	0.223	0.910	0.350	1.25	0.481	1.57	0.604
120	0.220	0.086	0.256	0.098	0.302	0.116	0.378	0.145	0.531	0.204	0.830	0.319	1.14	0.439	1.44	0.554
130	0.210	0.080	0.236	0.090	0.278	0.107	0.349	0.134	0.49	0.188	0.770	0.296	1.05	0.404	1.33	0.512
140	0.190	0.074	0.219	0.084	0.259	0.099	0.324	0.125	0.455	0.175	0.710	0.273	0.978	0.376	1.24	0.477

Table 8. Interrelationship of $\dot{V}_E$ and SO₂ concentration and D_{min} at various levels of %Δ SR$_{aw}$ for asthmatic subjects, exercising, unencumbered breathing (data derived from exponential best fit curve).

$\dot{V}_E$, L/min	0% SR$_{aw}$, D_{min} 30		10% SR$_{aw}$, D_{min} 42		25% SR$_{aw}$, D_{min} 53		50% SR$_{aw}$, D_{min} 61		100% SR$_{aw}$, D_{min} 69		200% SR$_{aw}$, D_{min} 77		300% SR$_{aw}$, D_{min} 81		400% SR$_{aw}$, D_{min} 84	
	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm	μg/L	ppm
10	3.00	1.15	4.20	1.62	5.30	2.04	6.10	2.35	6.90	2.65	7.70	2.96	8.10	3.12	8.40	3.23
20	1.50	0.577	2.10	0.807	2.65	1.02	3.05	1.17	3.45	1.33	3.85	1.48	4.05	1.56	4.20	1.62
30	1.00	0.385	1.40	0.538	1.76	0.677	2.03	0.781	2.30	0.885	2.55	0.985	2.70	1.04	2.80	1.08
40	0.750	0.288	1.05	0.404	1.33	0.512	1.53	0.588	1.73	0.665	1.93	0.742	2.03	0.781	2.10	0.810
50	0.600	0.231	0.840	0.323	1.06	0.408	1.22	0.469	1.38	0.531	1.54	0.592	1.62	0.623	1.68	0.646
60	0.500	0.192	0.700	0.269	0.883	0.339	1.02	0.392	1.15	0.442	1.28	0.492	1.35	0.519	1.40	0.538
70	0.429	0.165	0.600	0.231	0.757	0.291	0.871	0.335	0.986	0.379	1.10	0.423	1.16	0.446	1.20	0.462
80	0.375	0.144	0.525	0.202	0.663	0.255	0.763	0.283	0.863	0.332	0.963	0.37	1.01	0.389	1.05	0.404
90	0.333	0.128	0.466	0.179	0.589	0.226	0.678	0.261	0.766	0.295	0.855	0.329	0.900	0.346	0.933	0.359
100	0.300	0.115	0.420	0.162	0.53	0.204	0.610	0.235	0.690	0.265	0.770	0.269	0.810	0.311	0.840	0.323
110	0.272	0.105	0.382	0.147	0.482	0.185	0.550	0.213	0.627	0.241	0.700	0.269	0.736	0.283	0.764	0.294
120	0.250	0.096	0.350	0.135	0.442	0.170	0.510	0.196	0.575	0.221	0.642	0.247	0.675	0.260	0.700	0.269
130	0.231	0.089	0.323	0.124	0.410	0.158	0.470	0.180	0.531	0.204	0.592	0.228	0.623	0.243	0.646	0.248
140	0.214	0.082	0.300	0.115	0.379	0.146	0.440	0.168	0.493	0.19	0.550	0.212	0.579	0.223	0.600	0.231

protected when undergoing moderate to heavy exercise ($\dot{V}_E$ equal to 40 L/min), it can be seen (using the linear model) that the maximum SO_2 concentration can never be allowed to exceed 0.44 ppm (1.14 µg/L). Using the exponentially derived values (Table 8, Fig. 6), the SO_2 levels change accordingly, but the same principle applies. In this latter case, a 50% increase in SR_{aw} will be prevented at SO_2 concentrations below 0.59 ppm (1.53 µg/L) when the subjects exercise at the 40 L/min level.

Discussion

From this study there are a number of observations which can be made regarding increases in specific airways resistance in the exercising asthmatic exposed to SO_2 and the means by which these changes are viewed in attempts to establish protective ambient concentrations.

Initially, it can be concluded that there is a very consistent increase in specific airways resistance in these asthmatics as the rate of SO_2 expo-

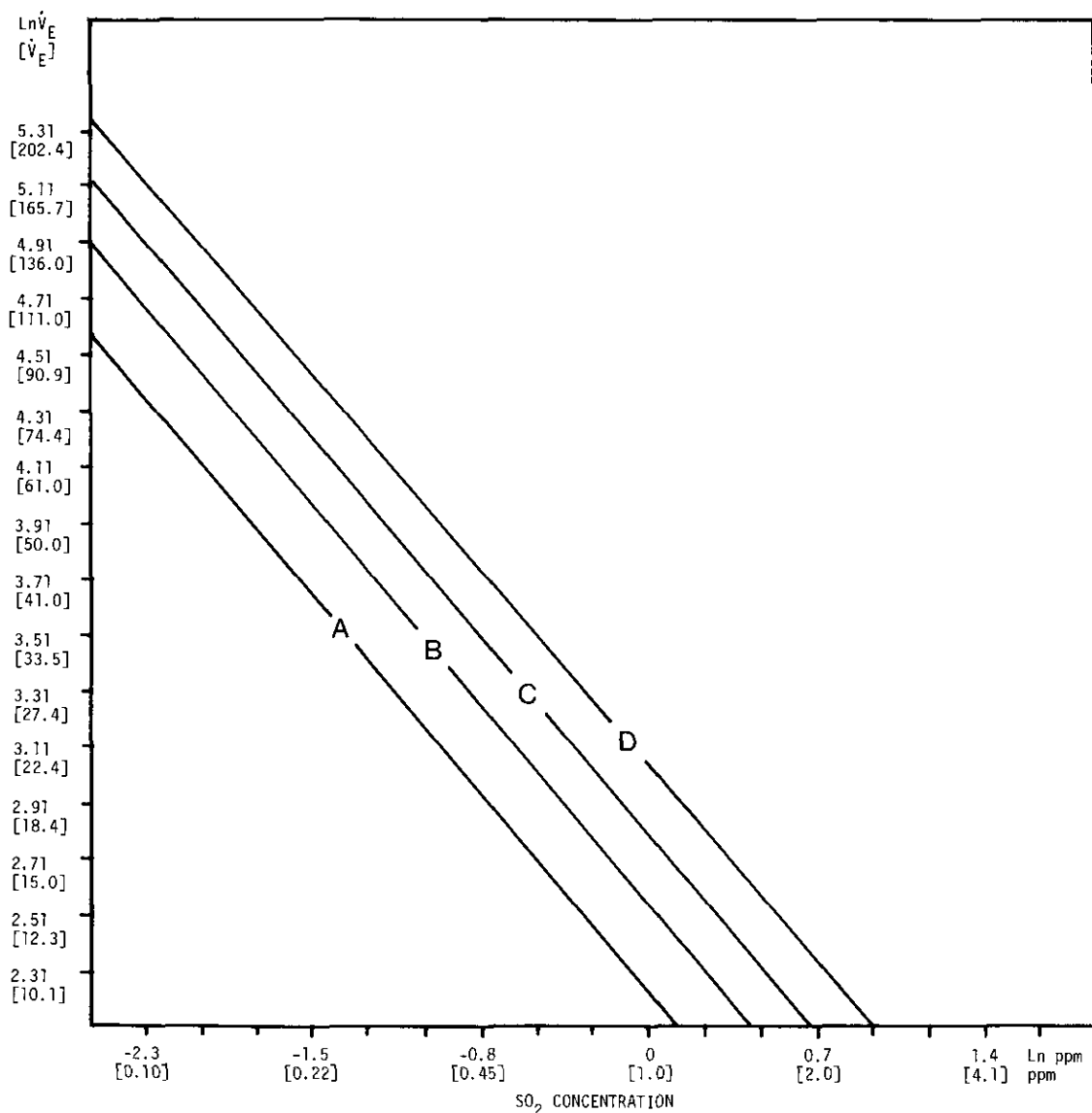FIGURE 5. Combination of SO_2 concentration and minute ventilation required to induce various levels of increase in SR_{aw} for unencumbered breathing: (A) 0% ΔSR_{aw}, D_{min} = 27 µg/min; (B) 25% ΔSR_{aw}, D_{min} = 36.2 µg/min; (C) 50% ΔSR_{aw}, D_{min} = 45.4 µg/min; (D) 100% ΔSR_{aw}, D_{min} = 63.7 µg/min. Data derived from linear best fit curve.

sure increases. This relationship has been found to be best described by an exponential equation suggesting that at the higher exposure rate (D_{min}) values, SR_{aw} increases more rapidly per unit increase in D_{min} than at lower exposure rates. The converse is true at the lower D_{min} values. Also, it has been determined that, while a simple linear relationship between D_{min} and $\%\Delta SR_{aw}$ can be shown to fit the data, it does so less strongly than the exponential equation and provides a generally more conservative model.

An important additional finding is that the observed increases in specific airways resistance that occur in these asthmatic subjects in response to SO₂ challenge are different in magnitude (but not in form) depending upon the mode of SO₂ exposure. Subjects forced to breath in an exclusively oral manner (mouthpiece with noseclip) demonstrate a consistently greater increase in SR_{aw} per unit increase in SO₂ exposure rate than their counterparts allowed to breath SO₂ in a less encumbered manner (oronasally). This observa-

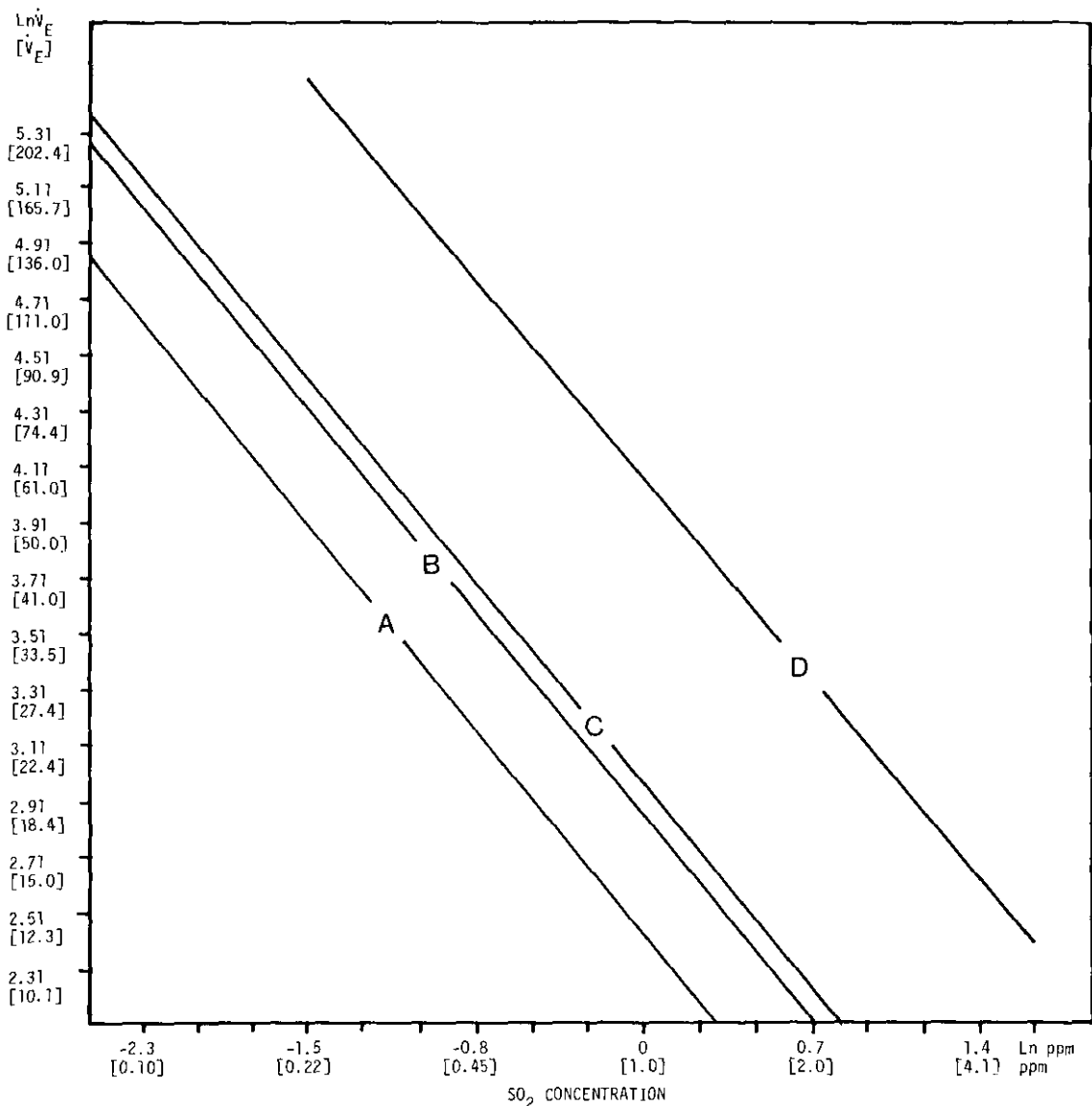FIGURE 6. Combination of SO₂ concentration and minute ventilation required to induce various levels of increase in SR_{aw} for unencumbered breathing: (*A*) 0% ΔSR_{aw}, $D_{min} = 30$ μg/min; (*B*) 25%, ΔSR_{aw}, $D_{min} = 53$ μg/min; (*C*) 50% ΔSR_{aw}, Dmin = 61 μg/min; (*D*) 100% ΔSR_{aw}, Dmin = 69 μg/min. Data derived from exponential best fit curve.

tion is not surprising, inasmuch as the forced oral (encumbered) breathers would be deprived of the filtering effect of the nose which is known to absorb SO_2 from the inhaled air and as such could be reasonably expected to receive a greater mass of SO_2 in their upper airways. Thus, although this finding is not surprising, it does pose serious questions as to the choice of data for extrapolation in a broader context.

Application of the model (linear or exponential) suggests also that future attempts to arrive at acceptable ambient levels must consider the influence of exercise level (activity patterns) more closely than in the past. We have shown that exercise level profoundly influences the extent of specific airways resistance increase which will occur at any SO_2 concentration. This is particularly true when data collected on small sets of subjects are to be used to provide quantitative insights into the expected changes in specific airways resistance of asthmatics in the general population experiencing changing exposures and manifesting changing activity patterns.

In the past, attempts to arrive at acceptable ambient levels have most commonly defined SO_2 exposure in terms of concentration alone (ppm or $\mu g/m^3$). While this approach may be applicable on singular sets of data obtained under closely controlled laboratory conditions, it is not sufficiently robust to account for the free-living circumstance.

Future attempts should define acceptable ambient levels as a combination of the degree of change in the effect parameters judged as desirable, as well as the concentration of SO_2 combined with level of activity which interact to produce this degree of change.

Conclusions

In this study we have demonstrated that by using data from a variety of controlled human exposure studies it is possible to relate increases in airways resistance systematically to the rate of SO_2 exposure in the exercising asthmatic. We have illustrated that the mode of exposure (oral vs. oronasal) greatly influences the degree of response in the asthmatic. Forced oral breathing consistently produces larger increases in SR_{aw} per unit increase in SO_2 exposure rate.

We have demonstrated further that the dose/effect relationship which describes the increases in SR_{aw} versus exposure rate (D_{min}) of SO_2 is most consistently exponential in character, but that a linear (more conservative) model also can be used to fit the data.

Using both the linear and exponential model, we have constructed a matrix which allows direct estimation of the combined $\dot{V}_E$ and SO_2 concentration (as ppm or $\mu g/L$) required to achieve various levels of airways resistance increase. At present we have explored only subjects exposed in an unencumbered (oronasal) manner. Future studies will explore these relationships in the asthmatic breathing exclusively orally.

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